UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/617,734	07/14/2003	Gregory Gregoriadis	G0365.0365/P0365	3606

7590 08/09/2007

DICKSTEIN SHAPIRO MORIN & OSHINSKY LLP
Edward A. Meilman
41st Floor
1177 Avenue of the Americas
New York, NY 10036-2714

EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
08/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/617,734	**Applicant(s)** GREGORIADIS, GREGORY	
	Examiner Richard Schnizer, Ph. D.	**Art Unit** 1635	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 27 July 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: _____.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Continuation of 3. NOTE: The scope of polypeptide antigens recited in claims 1 and 17 has been broadened from "an antigen or a fragment of an antigen of an infectious microbe, to any "target polypeptide". Also the scope of nucleic acids has been broadened from plasmid DNAs to any nucleic acid. Accordingly, neither Weiner nor Liu would be required to reject these claims under 103, necessitating new grounds of rejection over Felgner and Kirby alone. In claim 34 the scope of liposome forming components has been broadened beyond the group consisting of glycerides, cholesterol, and non-ionic and cationic surface active agents; and the scope of cationic components has been broadened beyond cationic surface active agents and cationic lipids.

ITEM 11 CONT'D

Applicant addresses the obviousness rejections at pages 8-16 of the response. At pages 8-12, Applicant argues that no prima facie case of obviousness has been made. First Applicant argues that Felgner teaches away from encapsulation of nucleic acids into the lumen of liposomes. Applicant states that it is unclear what is meant by the phrase "incorporating or encapsulating" at column 28, lines 27-34. Applicant also notes that the only exemplified composition of Felgner that contains nucleic acids is a complex in which DNA is adsorbed to the outside of the liposome. Applicant's attention is directed to column 15, lines 7-25 which states in part "the component lipids are dissolved in a solvent such as chloroform and the mixture evaporated to dryness as a film on the inner surface of a glass vessel. On suspension in an aqueous solvent, the amphipathic lipid molecules assemble themselves into primary liposomes. If other molecules are present in the aqueous solvent, such as, for example, a bioactive substance, these will be captured within the liposomes. Otherwise, empty liposomes will be formed." Felgner clearly considered nucleic acids to be bioactive agents (see e.g. column 7, lines 49-56, and column 8, lines 60-65), so this section fairly teaches the formation of liposomes with nucleic acids in the intravesicular space. There is no reason at all to assume that these active agents do not include the nucleic acids encoding immunogens disclosed at column 7, lines 49-56 or column 8, lines 5-8. Regarding the allegation that Felgner teaches away from the claimed invention by exemplifying complexes of lipids and nucleic acids, Applicant is reminded that disclosed examples and preferred embodiments do not constitute a teaching away from a broader

disclosure or nonpreferred embodiments. See MPEP 2123. The disclosure must be considered for all that it fairly teaches. In this case, contrary to Applicant's suggestion at page 10t of the response, the disclosure unambiguously discloses formation of liposomes comprising bioactive agents in their lumens, and also discloses that nucleic acids encoding immunogens are contemplated as bioactive agents. Absent some teaching that nucleic acids cannot be incorporated by the disclosed method, Felgner teaches toward encapsulating nucleic acids in liposomes, not away.

Applicant asserts that there is no reason to combine Kirby with Felgner. The stated motivation was of obtaining a greater proportion of oligo- and multilamellar vesicles which decrease the rate of loss of entrapped solutes (see paragraph bridging pages 982, and 983) and the expectation of excluding nucleases with greater success than unilamellar vesicles, thereby increasing the stability of the encapsulated nucleic acid. Against this, Applicant argues that one would not expect to obtain better protection against nucleases by entrapping than by complexing. For support Applicant relies on the specification at page 19, which Applicant states shows that entrapment gives slightly less access to nucleases than does complexation. This argument is unpersuasive for that reason, i.e. Applicant's example provides objective evidence that encapsulation provides better protection from nucle4ases than does complexation.

Applicant states at page 11 of the response that the Office appears to view that either Weiner or Liu provide a reason to apply Kirby to Felgner. This is incorrect. The Weiner and Liu references were relied upon to teach plasmid expression vectors and

encoded antigens not taught by Felgner. Accordingly a prima facie case for obviousness exists, and the references were properly combined.

At pages 12-15 of the results Applicant argues that the specification discloses unexpected results, referring for support to Table 5 at page 26. Table 5 discloses a comparison of immune responses obtained using similar amounts of plasmid DNA when either complexed, or entrapped into, liposomes of similar lipid composition (i.e. PC/DOPE/DOTAP liposomes). The results indicate a significantly greater immune response when the nucleic acids are encapsulated than when they are complexed. However, MPEP 716.02(d) indicates that in order to determine whether alleged unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. In this case, the evidence supports only a single combination of lipids, whereas the claims are not limited to this combination, and it is not clear that these results can be extrapolated to other combinations. The nonobviousness of a broader claimed range can be supported by evidence based on unexpected results from testing a narrower range if one of ordinary skill in the art would be able to determine a trend in the exemplified data which would allow the artisan to reasonably extend the probative value thereof. In this case there is nothing to indicate that one of skill could extrapolate the results to all other embraced lipid combinations.

Furthermore, with regard to rejections of claim 1, the secondary references were relied upon to teach particular sizes of liposomes (Kirby), and plasmids encoding an antigen of an infectious microbe (Weiner or Liu). There is no evidence of record to indicate that it is the size of the liposomes that provides the unexpected results, or that the unexpected results would be expected for the entire claimed range of sizes. Moreover, the size of the liposomes in Table 5 is not clear. However, it is evident from the results of Table 5 that use of a plasmid is not the source of the unexpected results because the same plasmid was used with both plasmid preparations. Thus it appears that the critical element leading to the difference in results for the two different preparations in Table 5 is the encapsulation of plasmid in one preparation, as opposed to plasmid adsorption to the surface of liposomes in the other preparation. This critical parameter is taught by Felgner, and the additions of selecting a particular size liposome, and selecting a plasmid vector to support antigen expression, are not considered to contribute to any unexpected result. For these reasons Applicant's arguments based on unexpected results are not persuasive and the rejections are maintained.

Regarding claim 7, Applicant argues that Collins teaches encapsulation by the process of microfluidization, whereas the instant claims require microfluidization of liposomes that already comprise encapsulated nucleic acids. This is unpersuasive. Collins teaches microfluidization after rehydration, as is claimed in claim 7. The fact that microfluidization might improve encapsulation by providing better mixing between the solute and lipids simply provides further motivation to employ this step. Evidence that encapsulation occurs in the absence of microfluidization comes from Kirby, as cited

in the rejection, and from Collins (see abstract). The rejection is proper and is maintained.

RICHARD SCHNIZER, PH.D.
PRIMARY EXAMINER